THE FORMULATION OF CARCINOGEN RISK STANDARDS ON THE BASIS OF THE CREDIBILITY OF RISK ASSESSMENTS

Roy E. Albert, M.D. & Rakesh Shukla, Ph.D.
Department of Environmental Health
University of Cincinnati College of Medicine

7-27-1992

ABSTRACT

This paper describes an approach to the formulation of carcinogen risk standards based on the level of credibility of the carcinogen risk assessments. Credibility is characterized as the product of the numeric ratings for the likelihoods that 1) a given agent is a human carcinogen and 2) that the linear non-threshold extrapolation model is valid for the given agent. The approach assumes that one hundred percent credibility in the risk assessment requires a hundred percent likelihood of a zero carcinogen effect. Below one hundred percent, the level of credibility is linearly related to the likelihood of a zero carcinogen effect. The likelihood of a zero carcinogen effect is then related to the fraction of the standard error of the estimated national cancer rate, for all types of cancer, by means of the Likelihood Ratio. The standard error of the cancer rate, expressed as the lifetime probability of dying from all forms of cancer, estimated either geographically (by states) or temporally (year-to-year), is 4×10^{-4}. The fraction of the standard error of the cancer rate associated with a given level of credibility in the risk assessment yields the risk standard for the given agent. Examples of risk standards for several carcinogens with varying degrees of risk assessment credibility are presented; their standards range from about 10^{-4} to about 6×10^{-4}.

INTRODUCTION

There is a difference between the legal and scientific mind-set. The law generally operates on the basis of black and white decisions. A person is guilty or not guilty. Medico-legal causality is established when the likelihood of an agent being the cause of a disease exceeds 50%. Science, by contrast, deals in the weight of evidence. A great deal of evidence is generally needed before a scientific hypothesis becomes accepted fact. In the regulatory arena the legal and scientific views collided in the early days of the US EPA, the mid-nineteen seventies. The circumstances involved the regulatory actions being taken against important pesticides, DDT, Heptachlor-Chlordane, Aldrin-Dieldrin, and Mirex. In the course of the hearings on these pesticides, the EPA sought to shorten the administrative hearing process by introducing, a series of cancer principles as matters of fact,i.e., which would not be arguable in court(1). These principles were simple declarative statements about cancer that raised the hackles of many scientists, e.g.," a carcinogen is any agent which increases tumor induction in man or animals"(2). Scientists were quick to point out that hormones and calories modulate tumor formation, and was the EPA going to regulate these modalities as carcinogens? The scientific community joined the Agro-chemical industry in attacking the EPA as, for example, in the Lancet editorial, entitled, " EPA's seventeen principles about cancer, or something"(3). After much internal debate, the EPA countered by declaring that it was going to regulate on the basis of weighing risks and benefits wherever it could, and in order to do so, it was going to evaluate the scientific data for putative carcinogens in a completely objective fashion, independent of the regulatory considerations. To accomplish this objective, it initiated Risk Assessment in a formalized way (4). The guidelines, first published in 1976, took the approach of setting up the format for an impartial display of the relevant scientific evidence for and against carcinogenicity, and the associated uncertainties(5). However, the uncertainties of the risk assessments, which arise from the limitations of the available evidence on given agents and the lack of understanding of carcinogenic mechanisms, has been a source of discomfort to the regulators. They naturally prefer to be told that a given agent is or is not a carcinogen rather than a **possible or probable** carcinogen. They prefer knowing how many people are going to die of cancer by exposure to a carcinogen rather than dealing with a **plausible upper limit estimate** of the incremental cancer mortality which is how EPA describes its risk estimates made with a low-dose linear non-threshold extrapolation model (6).

The traditional approach to standard setting is to apply arbitrary safety factors to the lowest observable toxic dose or the highest non-toxic dose. The resulting standards are deemed

safe and provide straightforward guidance to regulatory action. Risk Assessment, by introducing the scientific concepts of weight of evidence and its uncertainties and emphasizing uncertainty, has made regulatory decisions more complex.

No attempt has been made to utilize the uncertainty of risk assessment as the basis for the formulation of risk- based standards. The purpose of this paper is to explore a possible way to accomplish this end. Our approach is restricted to circumstances where there is no consideration of balancing risks and benefits, as with the clean up of hazardous waste sites. We also adopt the premise that in the absence of benefits, there is no acceptable risk; this is expressed by the NIMBY view (not in my back yard) about hazardous wastes. We use the credibility of the risk assessment, as the determinant of the stringency of the risk standard. The overall credibility of the risk assessment is the product of the credibility of the hazard assessment and the credibility of the linear low-dose extrapolation model. The overall credibility is related, in a one-to-one fashion, to the likelihood of a zero carcinogen effect. Given the variability of the cancer rate for the USA, measured geographically or temporally, the likelihood of a zero carcinogen effect determines the risk-based standard.

CREDIBILITY OF THE CARCINOGEN RISK ASSESSMENT

Two issues with any risk are how likely is it to occur, and what are the consequences if it does occur? Similarly, with carcinogen risk assessment, there are two components, the **Qualitative** aspect: how likely is the agent to be a human carcinogen? This is also called Hazard Assessment. And the **Quantitative** aspect: how much cancer would be produced by the agent for a given exposure? This involves Dose Response Assessment, and an Exposure Assessment.

In broad terms, the **Qualitative** aspect of carcinogen risk assessment involves a weight-of- evidence judgement based on molecular, cellular, and biochemical mechanisms, epidemiology, animal bioassay, and short-term tests. There are grades for the weight of evidence(7): A- a Definite human carcinogen on the basis of persuasive human and animal evidence of carcinogenicity; B- a Probable human carcinogen on the basis of at least two positive animal studies, and C- a Possible human carcinogen based on positive responses in a single animal species.

The **Quantitative** aspect of carcinogen assessment essentially involves the selection of a low dose extrapolation model, which determines the incremental risk in relation to the estimation of exposure. The multistage model dominates current usage, the most important aspect of which is its non-threshold low-dose linear character.

The summing up of the carcinogen risk assessment for a given agent, called Risk Characterization, involves the grading of the evidence for human carcinogenicity and a statement of potency which, in effect, is the low dose linear slope. For example, an agent might be categorized as (B) 10^{-2} / $\mu g/M^3$ for an airborne carcinogen meaning that it is a probable human carcinogen with a one percent lifetime incremental cancer risk for a lifetime average exposure of one microgram per cubic meter. The guidelines for risk assessment call for an explication of the uncertainties in the assessment but there is no guidance on how to factor the uncertainties into the risk assessment.

The approach proposed here formalizes uncertainty in terms of the credibility of the risk assessment. Credibility is characterized as the combination of the likelihood, from the qualitative assessment, that the agent in question is a human carcinogen and the likelihood, from the quantitative assessment, that the non-threshold low-dose linear extrapolation model is valid for the agent in question. Both factors have to be arrived at by the judgement of knowledgeable scientists and expressed in numeric form, e.g., from 0-1. The two factors are given equal weight and the overall credibility is the product of the numeric factors for both aspects of the risk assessment.

On the qualitative side, the weight of evidence for human carcinogenicity represents a judgement of whether the agent in question should be treated as a carcinogen or not. On the quantitative side, essentially the same holds true from a practical standpoint. The extrapolation models which are plausibly alternative to low dose linearity, e.g., the probit or dose square, produce negligible risk estimates compared to low dose linearity(8). The alternative to low dose linearity is virtual non-carcinogenicity due to negligible risks. Thus the credibility of the carcinogen risk assessment is effectively a judgement of how likely it is that the agent will behave as a human carcinogen at low doses.

INSIGNIFICANCE OF THE RISK ESTIMATE

The Likelihood Ratio concept is customarily used to determine in which population a data set is more likely to belong (9). Here, we use the **estimated** incremental cancer risk as if it were the observed data and use the Likelihood Ratio to obtain the odds that the incremental cancer risk could be interpreted as a zero carcinogen effect. This is illustrated in Figure 1. Let A represent the non-exposed population with the mean background cancer rate, m. Let B represent the exposed population with its mean cancer rate, v, which is the mean background rate plus the estimated incremental effect of the carcinogen; the incremental effect is v-m. The likelihood that population B is the same as A is given by the height of the intercept of v on the curve of

population A, namely, a/b. It can be seen that as the value of v-m decreases, the Likelihood Ratio increases such that when v and m coincide, the likelihood that population B is the same as population A reaches 1.0; this is the certainty of a zero carcinogen effect. The Likelihood Ratio can be expressed as a fraction of the standard error of the mean for population A. Based on an approximate Taylor series expansion, as described in the Appendix, the standard error fraction (S.E.F.) of population A = $[2(1-(a/b))]^{1/2}$ (10). Examples of the relationship between the Likelihood Ratio (zero carcinogen effect) and the standard error fraction are shown in Table 1. The 0.99 likelihood that population B is the same as population A occurs when the median of population B is separated from the median of population A by 0.14 standard error, assuming normal distributions with the same variability. It can be seen that the Likelihood Ratios, ranging from 0.99 to 0.05, cover approximately one order of magnitude in the standard error fraction: from 0.14 to 1.38.

Two approaches have been used to estimate the standard error in the cancer mortality rate for the USA: the state-to-state variability and the variability in the total number of cancer deaths from year to year(11). The geographic variability represents the average age-adjusted state cancer mortality rates for all types of cancer in the 20-year period from 1950 to 1969(12). These data were weighted according to the total number of cancer cases in each state over the 20-year period. The standard error, as a fraction of the mean for the combined sexes is 2×10^{-3}.

The temporal variability of the average annual age-adjusted mortality rates in the USA was determined for cancer of all types during the same 20-year period(13). The mean annual cancer rate was 1.8×10^{-3}. With the trend in the annual rates factored out by linear regression,the standard error was 2.9×10^{-6}; the fractional standard error (per unit mean) was 1.6×10^{-3}.

The fractional standard errors obtained by the two methods are very similar at 2×10^{-3} and 1.6×10^{-3} for an average 1.8×10^{-3}. The cancer risk equivalent to one standard error of the average cancer rate is the lifetime probability of dying of cancer (0.22) times the fractional standard error 1.8×10^{-3}; this cancer risk is 4×10^{-4}.

RELATION BETWEEN THE LIKELIHOOD OF A ZERO CARCINOGENIC EFFECT AND THE CREDIBILITY OF THE RISK ASSESSMENT

The relationship between the credibility of the risk assessment and the probability of a zero carcinogen effect, can be visualized as a plot of the two functions with both axes ranging from zero to one (Figure 2). At the upper end of the plot, the credibility of the risk estimate and the likelihood of a zero

effect are both 1.0 and at the lower end both approach zero. The question at issue is the shape of the relationship between the upper and lower extremes. An upwardly and a downwardly curving relationship would be more and less protective, respectively, as in Figure 2. In the absence of guidance from any analogous situations, we believe that the linear relationship is a reasonable, middle-of-the-road position. Thus, if we think that an agent has an equal likelihood of behaving like a carcinogen and a non-carcinogen, i.e., a credibility of 0.5, the likelihood of a zero carcinogen effect should be midway between a carcinogen and a non-carcinogen. We have therefore chosen a linear relationship between credibility and the likelihood of a zero incremental cancer risk for the formulation of risk-based standards.

ILLUSTRATIONS OF RISK-BASED CARCINOGEN STANDARDS

As an example of the process of formulating risk-based standards for carcinogens, we might take the cases of external exposure to gamma radiation, which is characteristic of whole body external exposure to long-lived fission products. This form of radiation involves high energy radiation with a linear energy transfer (LET) in the range of 0.1-0.3 kev. On the basis of animal and epidemiologic data the probability that such radiation is carcinogenic for humans is 1.0. However, the credibility of the linear low dose model is less sure. The results of an informal canvassing of six experts in radiation biology indicated a wide range of belief in the validity of the linear low-dose model, ranging from 1.0 to 0.2 with an average of 0.6. The one individual who was sure of the validity, based his argument on only the physical considerations of a single hit model for ionization damage of DNA. The others understood this, but qualified their judgements on the basis of biological considerations. Thus, the overall probability of the risk estimate being valid is 1.0 x 0.6, or 0.6. The likelihood of a zero risk, which is the ratio, a/b, is then 0.6. The S.E.F. equal $(2[1-0.6])^{1/2} = 0.9$. The risk-based standard equals the S.E.F.x the risk per S.E., or $0.9 \times 4 \times 10^{-4}$. The risk standard is therefore, 3.6×10^{-4}.

A risk based standard for radon might well involve a probability for human carcinogenicity of 1.0 and a probability of low dose linearity equal to 0.9. The ample epidemiological and animal evidence makes radon a certain human carcinogen. The high LET of the radiation from radon and its decay products, gives it a high rating for linearity. Thus, the certainty of the risk estimate might be 0.9, and the risk standard would be 1.8×10^{-4}.

Perchlorethylene, which is a widely used chemical in the dry cleaning industry, might have only a 0.25 probability of human carcinogenicity, because it induces only relatively benign tumors

in the liver and kidney of rodents and there is no persuasive epidemiological evidence for human carcinogenicity. Since the agent is not genotoxic, the credibility of the use of low dose linearity would also be low, perhaps 0.25. If this were the case, the overall credibility of the risk estimate would be 0.06; the S.E.F. would equal 1.38. The risk standard would be 5.5×10^{-4}.

Discussion

According to the Oxford English Dictionary, the term credible means "capable of being believed, trustworthy, reliable." They illustrate by quotation from Lithgow (1682), "It is holden to be so credible as if an oracle had spoken it." There is usage of credibility in decision making. In medicine, the credibility of a diagnosis gains strength when multiple tests point to the same diagnosis. Similarly, the credibility of a particular cause of a disease in epidemiologic studies becomes greater with the number of independent studies that show the same response under different circumstances. The fable about the boy who cried wolf is an example of the role of credibility in determining a social response. What is novel in this proposal, is that the credibility of the risk assessment is graded and related linearly to the likelihood of a zero carcinogenic effect. We posit that an agent, which is 100% certain to act as a human carcinogen at low doses, should have a 100% certainty of a zero risk. Conversely, as the credibility that an agent is a human carcinogen at low doses approaches zero, the requirement for a probability of a zero carcinogen effect should also approach zero. It is not illogical, that the degree of belief that an agent will act as a human carcinogen at low doses should correspond to the degree of belief in a zero carcinogen risk.

The calculated risk standards are relatively insensitive to differences in the degree of credibility in the risk assessment. This is largely because of the narrow range of variability in the cancer rate for the USA as a whole. This makes the standard error equivalent to a small increment in the cancer risk, namely 4×10^{-4}. By the same token, the risk standards are relatively insensitive to the shape of the curves, shown in Figure 2, relating the level of credibility of the risk assessment and the likelihood of a zero carcinogen effect. For the calculated risk standards to approach the level of 10^{-6}, there would have to be an extrordinarily high level of belief in the credibility of the risk assessment, namely, 99.9997%.

The EPA describes the results of the linear non-threshold extrapolation as a plausible upper limit assessment of risk, which is not likely to be exceeded but could be substantially lower(6). It is impossible to know what, if any, incremental effect on the cancer rate a carcinogen will have when the risk is below the detection limit of animal and epidemiologic studies.

We make judgements about the validity of such estimates based on existing scientific knowledge, but the validity cannot be established by direct observation. We can only put bounds on what the observed carcinogen effect would be even if the estimated increase were correct because of the variable forces that affect the background cancer rate and which are substantial in relation to the low-dose carcinogen effects. However, there is an equal likelihood that the response would be greater or smaller than predicted, so that the estimated increment is most probable.

The proposed approach is best used in terms of total cancer mortality. If specific types of cancer are used as an endpoint, for example, lung cancer, the variability does not increase a great deal, e.g., the fractional standard error increases from 1.8×10^{-3} to about 3.0×10^{-3}. However, the lifetime probability of death from lung cancer is much lower than from cancer as a whole and risk based standard would be correspondingly lower. It is an advantage, therefore, to use the total cancer experience in the country as a whole for several other reasons. The regulation of carcinogens is a public health program aimed at the reduction of the total burden of cancer. There is little preference in dying of any one form of cancer. Basing the variability of the cancer rate on national statistics is a conservative approach. The larger the population, the smaller the variability. Another conservative aspect of the proposed approach is that the entire population of the country is assumed to be exposed to each carcinogen. This compensates for the effect of multiple carcinogen exposures, since many carcinogens expose limited numbers of people.

The proposed approach has a number of advantages. 1- It uses the weight of evidence for human carcinogenicity, which at present, is ignored; e.g.,it does not seem appropriate to use the same standard for known human carcinogens and for those which are probable or possible human carcinogens. 2-The proposed approach uses scientific judgement about the credibility of low dose linearity, which is also presently ignored. The level of credibility for low dose linearity varies with the type of carcinogen; it is greater for high LET radiation than for low LET ionizing radiation and higher for genotoxic chemical carcinogens compared to those which are not. 3- The approach avoids use of a culturally based de minimis risk standard such as 10^{-6}, which has a relatively flimsy basis. 4- The approach does not tailor the risk to the size of the exposed population because when a standard is based on the induction of excess cancer cases, the risk to the individual can be high when small numbers of people are exposed. 5-In the case of chemical carcinogens that are identified by animal bioassay, the use of total cancers avoids the issue of where the cancers are likely to occur in humans.

A disadvantage of the proposal is the need for a delphic approach to determining the level of credibility in the risk assessment. But at least the credibility is based on scientific judgement about the nature of the evidence that supports carcinogenicity and low dose linearity. However, judgements depend on the status of scientific knowledge about low- dose mechanisms of carcinogenesis, and this is expected to increase with continuing research. The judgements may, therefore, have to be modified in time.

The use of the variability in the background of exposure to ionizing radiation(14) and chemicals(15) as the basis for formulating exposure standards that are small in relation to background variability is not new. However, the approach used here is different in that the background variability in cancer rates determines the odds of a zero carcinogen effect.

There are various forms of uncertainty in risk assessments. For example, there are uncertainties in the assessment of exposure or the statistical uncertainties in the extrapolation of data from the higher, observable dose range, to the low dose region. The only uncertainties that are included in the proposed approach are those that relate to the likelihood that the agent in question will behave as a human carcinogen.

The approach to relating the credibility of the risk assessment to the likelihood of a zero carcinogen effect on a proportional basis is contrary to the legal mind-set where judgements are dichotomous: agents are regulated either as carcinogens or as non-carcinogens. There is little flexibility to the regulatory process in this regard. The approach proposed here is consistent with the scientific tradition of making judgements on the basis of the weight of evidence.

APPENDIX

The Taylor series expansion is a generalized expression that provides the value of a function (e.g., a normal distribution) at points in the vicinity of the maximum, in terms of the distance from the maximum and the value of the function at the maximum. The Taylor series can be written as follows:

$$F(\theta) = F(\theta_o) + (\theta-\theta_o)\, F'(\theta_o) + 1/2(\theta-\theta_o)^2\, F''(\theta_o)$$

$$+ 1/3!(\theta-\theta_o)^3\, F'''(\theta_o)\ldots$$

Where $F(\theta)$ is the value of the function at θ; $F'(\theta)$ is the differential rate of change; $F(\theta_o)$ is the value of the function at the maximum, and $F'(\theta_o)$ is zero.

Neglecting the cubic term and higher order terms and since $(\theta-\theta_o)$ $F'(\theta_o)$ is zero, we have

$$F(\theta) = F(\theta_o) + 1/2\ (\theta-\theta_o)^2\ F''(\theta_o)$$

Rearranging terms, we have

$$2\ [F(\theta) - F(\theta_o)] = (\theta-\theta_o)^2\ F''(\theta_o)$$

Let $\frac{1}{F''(\theta_o)} = -W^2$ where W^2 is equivalent to the variance of θ_0 and therefore W is equivalent to the standard deviation of θ_o.

Rearranging terms, we have

$$[2(F(\theta_o)-F(\theta))]^{1/2} = \frac{\theta-\theta o}{W}$$

Let $F(\theta_o) = 1$ and let $\frac{F(\theta)}{F(\theta_o)} = \frac{a}{b}$ as in Figure 1, we get

$$\text{STANDARD ERROR FRACTION (SEF)} = \frac{\theta-\theta_o}{W} = [2(1-\frac{a}{b})]^{1/2}$$

REFERENCES

1. Pesticide Chemical News, 1975,**3**, p.10.

2. Council for Agricultural Science and Technology, Report No.54. The Environmental Protection Agency's Nine "Principles" of Carcinogenicity. January 19, 1976

3. The Lancet. Seventeen principles about cancer, or something. 1:571-573, March 13, 1976

4. Albert, R.E., R.E. Train and E. Anderson. Rationale Developed by the Environmental Protection Agency for the Assessment of Carcinogenic Risks. J. Natl. Cancer Inst. 58(5):1537-1541, (May, 1977).

5. United States Environmental Protection Agency.(U.S.EPA). 1976. Interim Procedures and guidelines for Health risk and Economic Impact Assessments of suspected Carcinogens. Federal Register 41:21402.

6. Anderson, E.L. and the Carcinogen Assessment Group of the U.S. Environmental Protection Agency. Quantitative Approaches in use to assess cancer risk. Risk Analysis 3:277, 1983

7. Albert, R.E. U.S. Environmental Protection Agency Revised Interim Guidelines for the Health Assessment of Suspect Carcinogens. In: Banbury Report 19: Risk Quantitation and Regulatory Policy, Cold Spring Harbor Laboratory, 1985, pp. 307-329.

8. National Research Council (NRC), 1983, Risk Assessment in the Federal Government. Managing the process. National

9. S.M. Goodman and R. Royall "Evidence and Scientific Research." Amer. J. Public Health 78, 1568-1574 (1988).

10. A.W.F. Edwards, Likelihood (Cambridge University Press, New York, 1976)

11. R.E.Albert and R. Shukla, The Use of Statistical Insignificance in the Formulation of Risk-Based Standards for Carcinogens. In : Comparative Risk Assessment. Ed. E. Richard Cothern. Lewis Publishers, Chelsea, Michigan. In Press.

12. U.S. Cancer Mortality by County: 1950-1969. U.S. Dept. of Health, Education, and Welfare. (PHS) T.J. Mason & F.W.McKay. DHEW Publication NO.(NIH)74-615.

13. Cancer Mortality in the United States: 1950-77. NCI Monograph 59 U.S. Dept. of Health and Human Services. PHS-NIH.

14. Adler, H.I. and A.M. Weinberg, "An Approach to Setting Radiation Standards," Health Physics 34: 719-720, (June 1978).

15. Travis, Curtis C. and Samantha A. Richter. On Defining a De minimis Risk Level for Carcinogens. De Minimis Risk, Contemporary Issues in Risk Analysis, Vol.2, 1987.

Table 1. THE RELATIONSHIP BETWEEN THE LIKELIHOOD RATIO (ZERO EFFECT) AND THE STANDARD ERROR FRACTION

Likelihood Ratio (Zero Effect)	0.99	0.95	0.90	0.75	0.50	0.05
Standard Error Fráction	0.14	0.32	0.46	0.71	1.00	1.38

FIGURE LEGENDS

Figure 1. Schematic of the Likelihood Ratio where a/b represents the likelihood of a zero carcinogen effect.

Figure 2. The relationship between the credibility of the carcinogen risk assessment and the likelihood of a zero incremental cancer risk

C:\ Risk

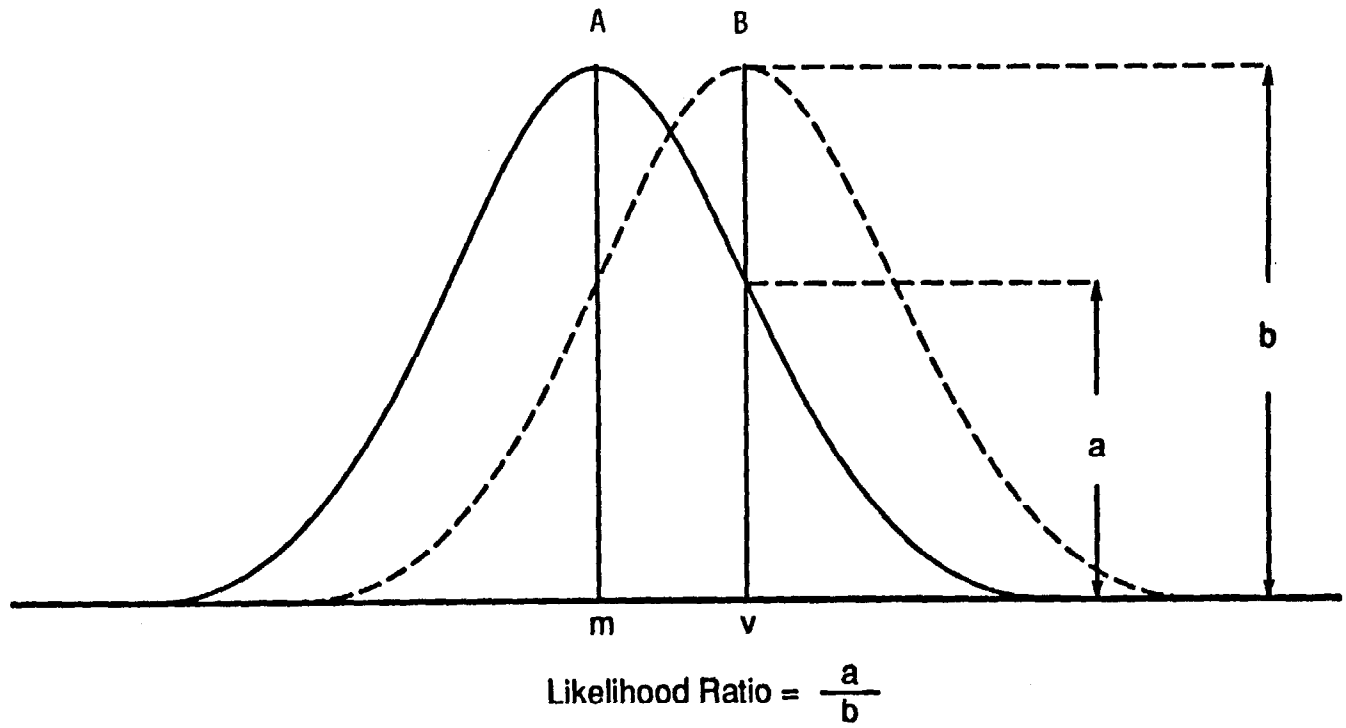

Figure 1. The Likelihood Ratio

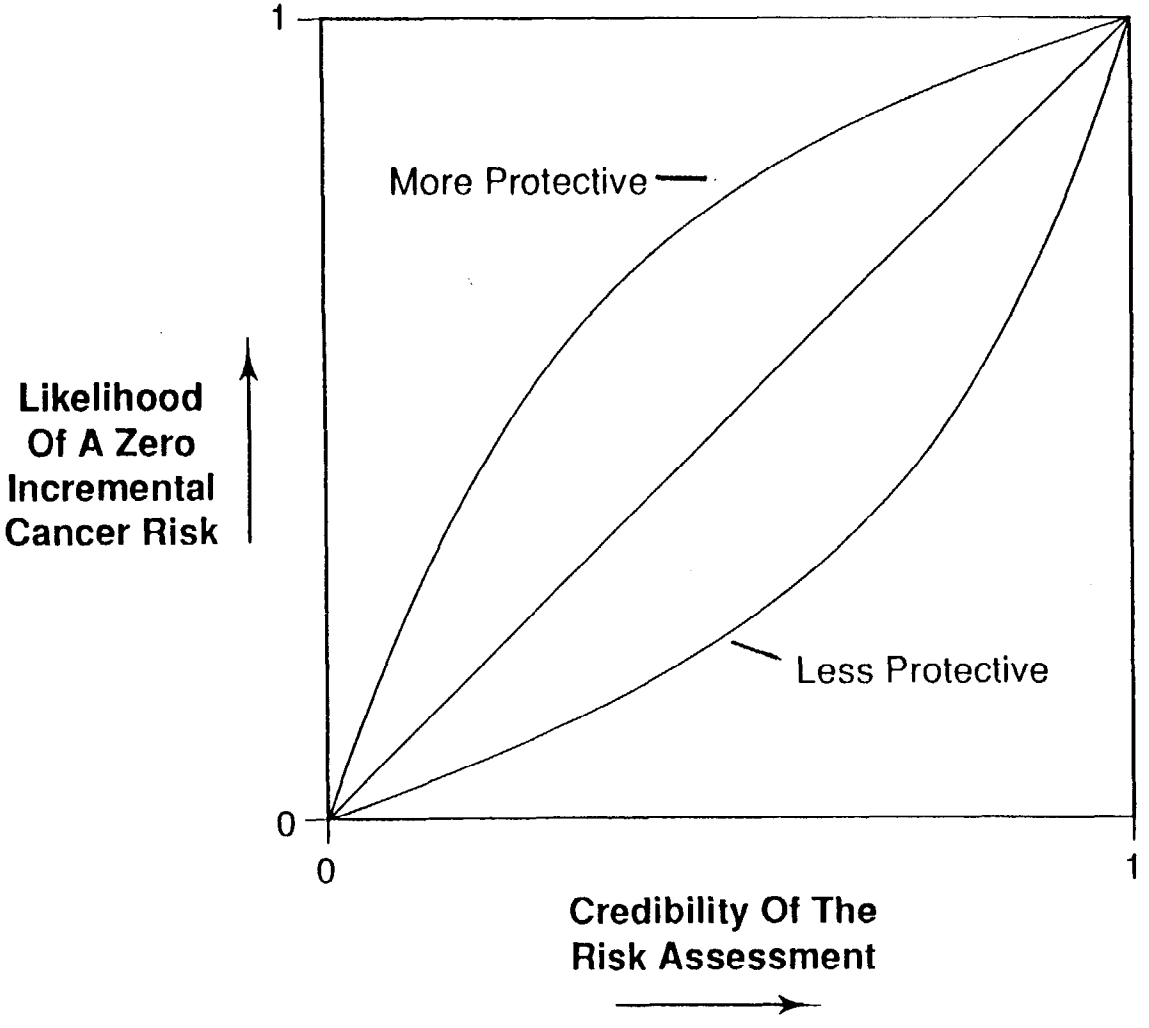
1
More Protective
Likelihood
Of A Zero
Incremental
Cancer Risk
Less Protective
0
0
1
Credibility Of The
Risk Assessment

Figure 2.